Tranexamic Acid for Trauma Patients: A Critical Review of the Literature

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Background: Tranexamic acid (TXA) is an antifibrinolytic that inhibits both plasminogen activation and plasmin activity, thus preventing clot breakdown rather than promoting new clot formation. TXA has been used around the world to safely control bleeding since the 1960s. A large randomized trial recently conducted in >20,000 trauma patients adds to the large body of data documenting the usefulness of TXA in promoting hemostasis.

Methods: We reviewed the literature describing use of TXA in a variety of settings including trauma.

Results: TXA has been safely used across a wide range of clinical settings to control hemorrhage. The results of a large, randomized, placebo-controlled trial support the use of TXA to treat bleeding trauma patients.

Conclusions: This inexpensive and safe drug should be incorporated into trauma clinical practice guidelines and treatment protocols. Further research on possible alternate mechanisms of action and dosing regimens for TXA should be undertaken. Concurrent to these endeavors, TXA should be adopted for use in bleeding trauma patients because it is the only drug with prospective clinical evidence to support this application.

Key Words: Tranexamic acid, Antifibrinolytic agents, Hemorrhage/drug therapy, Wounds and injuries/complications.

(*J Trauma.* 2011;71: S9–S14)

Trauma is the leading cause of death in persons younger than 40 years. Hemorrhage is the cause of death in 30% of these deaths.[1] The past decade has seen an explosion in research on the optimal management of hemorrhage in trauma. Recombinant human factor VIIa (NovoSeven) generated early excitement with Uri Martinowitz's observation that it could rescue patients on the verge of exsanguination.[2] A massive development effort on the part of Novo Nordisk (Princeton, NJ) ultimately led to disappointment as several pivotal clinical trials failed to meet primary endpoints, and the indications for use of NovoSeven approved by the U.S. Food and Drug Administration (FDA) were not expanded to include trauma. The hard-won experience gained by the U.S. Army in the conflicts in Iraq and Afghanistan has led to a renewed focus on blood products as the core of hemostatic resuscitation. Hemorrhage remains the leading cause of potentially preventable deaths on the battlefield and as such has been the subject of intensive research and development funding and effort.[3] Fixed-ratio transfusion, emphasizing the early use of plasma and platelets, has been associated with improved outcomes in retrospective studies and has been widely adopted in both civilian and military practice.[4–6] Recent efforts to enhance our understanding of the pathophysiology of trauma and thus facilitate the development of rational, targeted therapies have led to renewed interest in perturbations of the coagulation system. Brohi et al.[7] have shown that ~25% of seriously wounded trauma patients present with abnormal international normalized ratios and that this state is associated with increased morbidity, mortality, and blood product use. Gando et al.[8] have reported similar findings. The molecular underpinning of this state, which has most recently been termed "acute coagulopathy of trauma", appears to involve activation of protein C and the consequent inactivation of factors V and VIII as well as the de-repression of fibrinolysis by inactivation of plasminogen activator inhibitor-1.[9] These findings and related research programs will undoubtedly lead to improvements in our armamentarium. However, until recently, trauma physicians have been frustrated by the lack of a single pharmacologic intervention for the management of hemorrhage that could be prescribed with confidence grounded in the results of a large randomized controlled trial. It is in this context that we consider the results of the landmark trial, Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2), which tested the safety and efficacy of tranexamic acid (TXA) in trauma resuscitation. The results of this trial, recently published in *The Lancet*,[10] showed that use of TXA resulted in a reduction in all-cause mortality and death as a result of bleeding.

Chemistry and Pharmacology

TXA is an antifibrinolytic that inhibits both plasminogen activation and plasmin activity, thus preventing clot break-down rather than promoting new clot formation. TXA (trans-4-[aminomethyl]cyclohexanecarboxylic acid) is a small molecule (MW, 157.2), inhibitor of plasminogen activation and inhibitor of plasmin activity. It occupies the lysine-binding sites on plasminogen, thus preventing its binding to lysine residues on fibrin. This reduces plasminogen activation to plasmin. Similarly, blockade of lysine-binding sites on circu-

Submitted for publication April 18, 2011.
Accepted for publication April 22, 2011.

From the U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas.
Supported by U.S. Army.
The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army or Department of Defense.
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DOI: 10.1097/TA.0b013e31822114af

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 JUL 2011	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Tranexamic acid for trauma patients: a critical review of the literature	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Cap A. P., Baer D. G., Orman J. A., Aden J., Ryan K., Blackbourne L. H.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a REPORT	b ABSTRACT	c THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**6**	

lating plasmin prevents binding to fibrin and thus prevents clot break-down. TXA is 10 times more potent in vitro than an older drug of the same class, aminocaproic acid. At therapeutically relevant concentrations, TXA does not affect platelet count or aggregation or coagulation parameters. It is excreted largely unchanged in urine and has a half-life of about 2 hours in circulation. Dosing should be adjusted for renal impairment, but no adjustment is needed for hepatic impairment.[11] TXA (intravenous trade name: cyklokapron) is supplied in ampoules of 1,000 mg in 10 mL water for injection. Dosing is typically 10 mg/kg body weight intravenously given 3 to 4 times daily for 2 to 8 days. It is infused at a maximum rate of 1 mL per minute. More rapid injection has been reported to cause hypotension.[11] TXA is also available in tablet form (oral trade name: Lysteda). It is given orally as two 650 mg tablets three times a day for a total daily dose of 3,900 mg for a maximum of 5 days.[12] TXA is stored at room temperature.

Food and Drug Administration Approval

Intravenous administration of TXA was approved by the FDA in 1986 for prevention or reduction of bleeding in patients with hemophilia undergoing dental procedures.[13] The FDA approved use of the oral form of TXA to control heavy menstrual cyclic bleeding in 2009.[14] Adverse events associated with TXA use have been reported. These include acute gastrointestinal disturbances (nausea, vomiting, and diarrhea, generally dose related), visual disturbances (blurry vision and changes in color perception, especially with prolonged use), and occasional thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, generally observed in the setting of active intravascular clotting such as thrombotic disseminated intravascular coagulation).[11,12] Its use is thus contraindicated in the settings of acquired defective color vision and active intravascular clotting. TXA should be used with caution in the setting of urinary tract bleeding since ureteral obstruction due to clotting has been reported. TXA should not be given with activated prothrombin complex concentrate or factor IX complex concentrates because these concentrates may increase the risk of thrombosis.[15]

TXA Historical Background

TXA was first described in 1966.[16] Its use has been extensively reviewed by several authors. Nevertheless, several significant milestones in the drug's development should be considered to set the context for evaluation of the CRASH-2 trial. The first clinical trial reporting the use of TXA in controlling menstrual bleeding was published in 1968, and multiple clinical trials documenting its safety and efficacy for this indication have been recently reviewed.[17,18]Its use in managing hemorrhage after dental extraction in patients with hemophilia was described in 1972.[19] Throughout the 1970s, use of TXA to control bleeding was described in a number of clinical settings, including pediatric urinary tract surgery,[20] ruptured intracranial aneurysms,[21] oral surgery[22] gynecologic surgery,[23] treatment of hereditary angioneurotic edema,[24] upper gastrointestinal hemorrhage,[25,26] and traumatic hyphema.[27]

TXA use expanded over the next 20 years to include wide application in hemophilia, von Willebrand disease, refractory thrombocytopenia, and dysfunctional uterine bleeding. TXA was adopted to treat the hyperfibrinolysis associated with cardiopulmonary bypass and liver transplantation and has been proven to reduce blood loss and need for transfusion in these settings.[28] Concerns regarding risk of thrombosis with use of TXA have not been substantiated in clinical trials.[15] TXA has been shown to reduce bleeding and transfusion requirements without increasing thromboembolic complications in patients undergoing hip or knee arthroplasty despite the high baseline thrombotic risk in this population.[29]

TXA has also been studied in patients with subarachnoid hemorrhage (SAH). TXA was shown to reduce bleeding but increase cerebral ischemia, possibly because of vasospasm or increased microvascular thrombosis. Because TXA use had no effect on mortality or quality of life in these studies, its use is not recommended in this population.[30] At this time, there is no role for TXA or other antifibrinolytics in managing SAH. It should be noted that treatment with TXA in these studies was modeled on the prolonged dosing (3–4 times per day for 2–8 days) used in hemophilia. A dosing regimen shorter in duration might avoid this outcome and remains a topic for further investigation.

Pivotal Trauma Trial Synopsis and Methodology

CRASH-2 was a large, randomized, double-blinded, placebo-controlled, multicenter clinical trial. In this trial, 20,211 adult trauma patients in 274 hospitals in 40 countries with, or at risk of, significant bleeding were randomized to either TXA or placebo administered as a loading dose of 1 g over 10 minutes followed by an infusion of 1 g over 8 hours. The primary outcome was death in hospital within 4 weeks of injury. Secondary outcomes included vascular occlusive events, transfusions, and surgical interventions. Patients were randomized and treated within 8 hours of injury. Patients were excluded from randomization only if the treating physician considered the patient to have either a clear indication for use of TXA or a clear contraindication.

The authors reported that TXA use resulted in a statistically significant reduction in the relative risk (RR) of all-cause mortality of 9% (14.5% vs. 16.0%; RR, 0.91; confidence interval [CI], 0.85–0.97; $p = 0.0035$). This 1.5% absolute risk reduction means that one would have to treat 67 trauma patients with TXA to prevent one from dying of any cause (number needed to treat = 1/absolute risk reduction; note that number needed to treat depends on baseline risk in a given population: a higher baseline risk results in a lower number needed to treat for a given reduction in RR). The authors also reported a reduction in RR of death as a result of bleeding of 15% (4.9% vs. 5.7%; RR, 0.85; CI, 0.76–0.96; $p = 0.0077$). Similarly, they reported an RR reduction in death as a result of bleeding on the day of randomization of 20% (2.8% vs. 3.5%; RR, 0.80; CI, 0.68–0.93; $p = 0.0036$). It was in this group of most severely injured patients that use of TXA was associated with the greatest reduction in risk of death. Further subgroup analysis suggested that the benefit of TXA was greater in patients treated within 3 hours of injury compared with those treated later and in patients with a presenting systolic blood pressure of $\leq$75 mm Hg compared with those with normal systolic blood pressures. There was no

difference in rate of vascular occlusive events between the two arms of the study (1.7% for TXA vs. 2.0% for placebo, $p = 0.084$). No unexpected adverse events were reported. There were no differences in need for transfusion or operation between the two arms (blood product transfused in 50.4% of patients for TXA vs. 51.3% for placebo, $p = 0.21$; any operation in 47.9% of patients for TXA and 48.0% for placebo, $p = 0.79$).

Scientific Merit

The CRASH-2 trial was a randomized, double-blinded, placebo-controlled trial with intention-to-treat analysis. This type of analysis is considered the highest level of evidence in clinical research. Randomization reduces bias by generating treatment and non-treatment groups that are comparable at the start of the study. This in turn reduces the risk that an imbalance between the groups could confound the results. The *Lancet* study treatment and placebo groups were well balanced on a range of prognostic factors. The randomization and blinding procedures also ensured that participating clinicians did not have advance knowledge of whether an individual patient was receiving the treatment or the placebo.

The intention-to-treat approach is the method recommended by the FDA for use in clinical trials.[31] The strength of this method is that data are analyzed for all subjects that the investigator intended to treat and study groups are compared in terms of the treatment group to which they were originally assigned. This approach helps to preserve the value of the randomization. If patients who are originally randomized are eliminated from the analysis, the residual groups may no longer be comparable. Of particular concern, if the patients who remain are those who were likely to have a better outcome, the efficacy of the treatment may be overstated. Intention-to-treat analysis was possible in the CRASH-2 trial because of the high follow-up rate and low percentage of missing data.

The *Lancet* study had a very large and diverse study population and was conducted in a range of different healthcare settings. This increases the degree to which these results may be generalized and suggests that TXA could be used widely in trauma.

Research Ethics

No ethical concerns have been identified in the CRASH-2 study design, collaborative arrangements, funding, or research subject protection measures. The drug manufacturer, Pfizer, was clearly listed as a source of funding, which was largely limited to providing the study drug. Nonprofit research organizations provided most of the funding for the study. The Writing Committee had access to all the data in the study, and none of its members declared conflicts of interest. The trial was performed with local Institutional Review Board review and approval. Informed consent was sought where possible in accordance with local consent policies, thus ensuring the highest degree of research subject protection possible in such a study.

Critical Discussion

As the only large, prospective randomized trial to demonstrate an all-cause 30-day mortality benefit in trauma patients, the CRASH-2 study has been the subject of intense interest and discussion. This discussion has centered on several issues. The CRASH-2 design has been criticized for allowing the determination of patient eligibility to depend on the treating physician's uncertainty as to whether or not the patient might benefit from TXA (patients excluded only for clear indication for use or clear contraindication). Although this design may seem to introduce excessive physician discretion in determining patient eligibility, it should be clear that clinical equipoise could be the only ethical basis for enrolling patients in the study. Furthermore, a clear indication for use of antifibrinolytics would rely on either a history of recent fibrinolytic use (very unlikely in a trauma population) or some laboratory evidence of hyperfibrinolysis (e.g., thromboelastography or rotational thromboelastometry data showing a fibrinolysis tracing or serial laboratory values indicating accumulation of D-dimer and/or fibrinogen degradation products).[32,33] Clear laboratory evidence of hyperfibrinolysis is not commonly available during initial trauma evaluation when decisions to randomize would occur (particularly in many of the hospitals participating in the trial). In short, it is unlikely that these exclusion criteria had a significant impact on patient accrual. In any case, excluding patients with clear evidence of hyperfibrinolysis, which TXA was designed to treat, would be expected to reduce the power of the study to show a benefit for the drug. The fact that a benefit was observed despite this exclusion suggests a strong treatment effect.

As to the concern about excluding patients with a clear contraindication to TXA use, such as obvious thrombosis, this too, in all likelihood, led to a relatively small impact on patient accrual. It is far more common for trauma patients to present with bleeding than with thrombotic disseminated intravascular coagulation or pulmonary embolism. In any case, these complications are not typically manifest in the 8-hour window for randomization in the trial. One could argue that systematic exclusion of patients with evidence of thrombosis would bias the study toward exaggerating the safety profile of TXA. Although this is true, it also makes sense that physicians would not use a drug designed to stop bleeding in patients who were clotting excessively and not bleeding.

Critics have also noted that it would have been helpful to know outcomes for patients with traumatic brain injuries (TBIs) because TXA has not proven to be beneficial in SAH. The CRASH-2 trial did not exclude TBI patients, but separate detailed outcomes for this cohort were not reported. Such an analysis would be informative. It is worth noting, as discussed above, that the relative contraindication to using antifibrinolytics in SAH was known before the initiation of CRASH-2 (2005) and that TXA had not been extensively studied in TBI.[34] Thus, it is possible that treating physicians tended to exclude patients with TBI from trial enrollment. Nevertheless, ~18% of patients had a Glasgow coma scale (GCS) score of 3 to 8 (17.8% for TXA, 18.2% for placebo), probably indicating severe TBI; and 13.4% had GCS scores of 9 to 12 ($p > 0.05$, not significant, for both groups), indicating moderate TBI. Mild or no TBI (GCS, 13–15) was present in 68.7% (TXA) and 68.3% (placebo). Although GCS

scores can be depressed for a variety of reasons such as global hypoperfusion, it would be reasonable to expect that a substantial fraction of trauma patients with depressed GCS had in fact sustained a TBI. The authors do report that death from head injury was the same in both groups (6.0% for TXA and 6.2% for placebo; RR, 0.97; CI, 0.87–1.08, $p = 0.6$). They also report that stroke rates (0.6% for TXA and 0.7% for placebo) and neurosurgery rates (10.3% for TXA and 10.5% for placebo) were similar between the groups. These data are reassuring; if a major safety concern were present for perhaps one third of the patients in the trial (those with depressed GCS among whom TBI patients are common), a negative effect on outcomes would be expected.

Trauma patients who receive a massive transfusion ($\geq$10 units of blood within 24 hours) are of particular interest because of their high observed mortality rate and the potential for therapeutic innovations to impact this mortality. The authors did not present subgroup analyses describing the experience of patients receiving massive transfusion or suffering massive hemorrhage nor did they collect laboratory data to monitor changes in coagulation function. It would have been helpful to have this data to fully understand the beneficial actions of TXA and monitor its activity, especially because TXA did not significantly reduce the rate of transfusion in this study (50.4% vs. 51.3%; RR, 0.98; CI, 0.96–1.01, $p = 0.21$), as it has in other settings, such as cardiac operation. This could have been due to the inherent challenges of estimating blood loss and need for transfusion in trauma patients or perhaps because decisions to randomize patients were taken at the same time as or after decisions to administer blood products. It is also possible that TXA-treated patients received more transfusions simply because they were more likely to survive long enough to receive them. This "survivor bias" makes it very difficult to use blood product transfusion as a metric for evaluating the efficacy of a product used to treat severe hemorrhage in trauma or to use quantity of products transfused as a surrogate for hemorrhage volume. In any case, correlative laboratory data would have enriched our appreciation of the study findings. It is possible that TXA exerted its beneficial effects by an unexpected mechanism, which might have been uncovered by detailed laboratory data. There are several possible alternative mechanisms for TXA's effects, some of which were reviewed by Levy in the editorial accompanying publication of the CRASH-2 results.[35] Laboratory data might also have informed possible refinements to the dosing regimen, which, although designed to improve hemostasis in the early postinjury period without increasing unduly prothrombotic risk, represents a significant departure from typical TXA dosing. The possibility that a different dosing regimen, possibly based on optimizing an unexpected mechanism of action, might have resulted in even better trial outcomes presents opportunities for further research. It is worth recalling, however, that the authors reported a 20% reduction in RR of death as a result of hemorrhage on the day of randomization, indicating that TXA had a potent effect on the most severely hemorrhaging patients. Also, the broad range of patients included in the study adds to confidence in the safety and efficacy of TXA. It will nonetheless be useful to identify the patients who might benefit the most from this intervention. Subgroup analyses may be forthcoming in future publications from the study group.

Finally, the authors have been criticized for not using a trauma scoring system for characterizing their study groups. They anticipated this criticism and present their rationale for not using these systems on the study's Web page.[36] They did not use the injury severity score because it is applied in retrospect and would thus not be helpful in the study of an intervention that is applied before all injuries are even defined. In addition, the injury descriptions used in the injury severity score do not capture the degree of hemorrhage associated with the injury. They did not use the revised trauma score because it gives a heavy weight to level of consciousness and does not define a group that has significant bleeding. The authors also felt that the added training requirements and complexity to the patient entry process would be excessively burdensome.

The preceding discussion notwithstanding, it is clear that this study was performed in a rigorous manner that reflected real-world clinical practice across a wide variety of settings, including austere environments. CRASH-2 provides Level I evidence for the use of TXA to reduce mortality in trauma patients. The inclusion criteria for this study were clinical, not laboratory based, and very broad. As a result, the population truly at risk for hemorrhagic death was much smaller than the overall study population, as further evidenced by the fact that slightly fewer than 50% of patients in each arm underwent surgical interventions. The fact that a significant reduction in death as a result of hemorrhage was observed is therefore even more remarkable and suggests an important treatment effect in critically wounded patients.

Implementation of CRASH-2 in Military and Civilian Trauma Systems

TXA is safe and inexpensive. For military use, the current U.S. Department of Defense formulary cost is $39.12 per 10 mL vial containing 1 g of TXA, or about $80 for the regimen used in the trial (P. E. Scheller, June 2010, personal communication). For civilian use, the cost at CVS Pharmacy is $101.99 per 10 mL vial containing 1 g of TXA, or ~$204 for the regimen used in the trial (CVS Pharmacy staff, July 2010, personal communication). It is currently the only drug shown by a prospective, randomized controlled trial to be associated with an all-cause and bleeding death mortality benefit in trauma. TXA has been used for the past year in the United Kingdom's military massive transfusion protocol and in prehospital care of combat casualties (T. Hodgetts, June 2010, personal communication). It is also being incorporated into civilian resuscitation protocols in some centers in both the United Kingdom (used in London, K. Brohi, August 2010, personal communication) and the United States (used at Massachusetts General Hospital, H. Alam, panel discussion, American Association for the Surgery of Trauma, October 2010). A recent study suggests that TXA may be particularly cost effective in the resource-constrained environments of developing countries.[37]

Risks Associated With Broad Adoption of TXA

Use of this drug in conjunction with procoagulant drugs sometimes administered to trauma patients, such as recombinant factor VIIa (Novoseven) or activated prothrombin complex concentrate, could result in thrombotic complications. Of note, only 17 patients enrolled in the CRASH-2 trial received Novoseven (13 in the TXA group and 4 in the placebo group). It is also possible that a subgroup of patients not identified in the CRASH-2 trial, such as those with TBI, may be at particularly high risk of thrombotic or other complications if treated with TXA. It is worth noting that the CRASH-2 collaborators are planning a specific analysis of outcomes in patients with TBI that may address this concern (CRASH-2 Intracranial Bleeding Study, www.controlled-trials.com/ISRCTN86750102, www.hta.ac.uk/project/2096.asp). Finally, it is possible that some patients treated with TXA will derive no benefit and that the health-care system will be burdened by unnecessary costs. It is very reassuring, however, that no increase in vascular occlusive events was observed in this study, despite the significantly increased baseline risk of such complications in this population. In particular, it has been demonstrated that non-bleeding critically ill trauma patients are hypercoagulable, and at particularly high risk of venous thromboembolism.[38] Despite the likely large number of such patients in CRASH-2 (only about half of study patients required a transfusion), there was no difference in the rate of venous thromboembolism. It is true that the rate of deep-vein thrombosis reported is difficult to interpret because of the lack of a consistent screening protocol and the variable clinical importance of this complication. However, the rates of myocardial infarction, stroke, and pulmonary embolism may be more informative. These complications are relatively simple to diagnose and are clinically important. None of these complications were more common in the treatment arm, whereas myocardial infarction was significantly less common in the TXA group ($p = 0.035$). These data strongly argue against a safety problem with respect to vascular occlusive events.

Potential Benefits of TXA Adoption

Approximately 80% of combat casualties with potentially survivable injuries die from hemorrhage. We will assume that TXA would be administered to hemorrhaging patients and that a reasonable identifier for such patients would be transfusion of blood products. A recent study by Wade et al.[39] reported that between October 2003 and June 2009, the records of 18,638 trauma patients were entered into the U.S. military's Joint Theater Trauma Registry. Of these, 2,050 received transfusions and met the inclusion criteria for the study (51 received transfusions but were excluded). The overall mortality rate for this cohort was 14.6%, similar to that reported by the CRASH-2 investigators. If these patients had been treated with TXA, and we were to apply the all-cause mortality RR reduction observed in CRASH-2 of 9%, we would expect a transfused combat casualty mortality rate of 13.3% instead of 14.6%. That would translate to 26 extra lives saved at a cost of about $6,300 per life. (This cost was calculated as follows: $164,000 to treat all 2,050 patients requiring transfusion, at $80 per patient for the cost of the CRASH-2 regimen. The expected number of fatalities would be 299 in the untreated group and 273 in the TXA group, for a net benefit of 26 lives saved; $164,000 divided by 26 yields $6307.69) For perspective, the cost to the U.S. military of procuring 1 unit of packed red blood cells is ~$100 (F. Rentas, Armed Services Blood Program Office, July 2010, personal communication). This amount does not include the costs of blood storage and shipment to theater, disposables, and nursing time associated with blood administration or blood unit cross-matching. The costs of administering TXA are thus substantially lower than the costs of administering 1 unit of red blood cells. Furthermore, TXA given intravenously, or possibly by another route such as intraosseously, offers the opportunity to begin hemostatic resuscitation at the earliest possible moment, in the prehospital setting, where the greatest potential for improving outcomes exists.

Trauma Pharmacopeia, Version 1.0

Targeted pharmacologic therapies that reduce trauma mortality as a result of bleeding have proven elusive until now. As we develop a deeper understanding of acute coagulopathy of trauma, we will undoubtedly make progress toward the goal of individualized, rational therapy. In the meantime, the CRASH-2 investigators have provided us with a first-generation armament: TXA. Although not a panacea, it represents a first step in the right direction. This inexpensive and safe drug should be incorporated as described in CRASH-2 into trauma clinical practice guidelines and treatment protocols now. Further research on possible alternate mechanisms of action and next-generation dosing regimens for TXA should begin while identification of new pathophysiological targets and development of new drugs continue. These endeavors should not delay implementation of our only proven drug therapy.

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